(FILE 'HOME' ENTERED AT 11:12:52 ON 01 JUN 2003)

FILE 'REGISTRY' ENTERED AT 11:20:19 ON 01 JUN 2003

L1 SCREEN 1006
L2 STRUCTURE UPLOADED
L3 QUE L2 AND L1
L4 50 S L2
L5 SCREEN 1006
L6 STRUCTURE UPLOADED
L7 QUE L6 AND L5
L8 0 S L7
L9 8 S L7 FULL

FILE 'CAPLUS, USPATFULL' ENTERED AT 11:34:05 ON 01 JUN 2003

L10 6 S L9

FILE 'BEILSTEIN' ENTERED AT 11:38:08 ON 01 JUN 2003

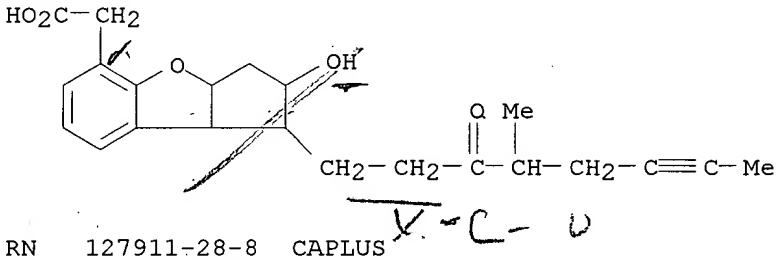
L11 0 S L6
L12 0 S L6 FULL

L10 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:911374 CAPLUS
DOCUMENT NUMBER: 124:25112
TITLE: Radioimmunoassays of beraprost isomers
AUTHOR(S): Mouren, M.; Touyer, G.; Verdier, P.
CORPORATE SOURCE: Department Pharmacokinetics and Metabolism, Roussel-Uclaf, Romainville, 93235, Fr.
SOURCE: Synthesis and Applications of Isotopically Labelled Compounds 1994, Proceedings of the International Symposium, 5th, Strasbourg, June 20-24, 1994 (1995), Meeting Date 1994, 459-61. Editor(s): Allen, John; Voges, Rolf. Wiley: Chichester, UK.
CODEN: 61UMAF
DOCUMENT TYPE: Conference
LANGUAGE: English

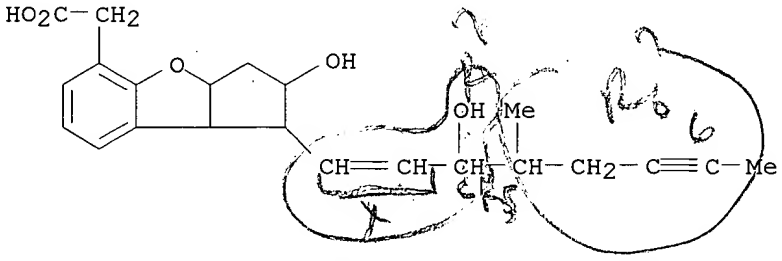
AB Beraprost is an equal mixt. of two racemates (four isomers), APS-314 d,l and APS-315 d,l. Sensitive and specific RIAs have been developed to det. the plasma concns. of each isomer. Antibodies to the isomers were raised in rabbits immunized with beraprost conjugated to bovine serum albumin. Radioiodinated derivs. of each isomer were used as radioligands.

IT **127833-77-6 127911-28-8**
RL: ANT (Analyte); ANST (Analytical study)
(beraprost racemic anal. in plasma by RIA)

RN 127833-77-6 CAPLUS
CN 1H-Cyclopenta[b]benzofuran-5-acetic acid, 2,3,3a,8b-tetrahydro-2-hydroxy-1-(4-methyl-3-oxo-6-octynyl)- (9CI) (CA INDEX NAME)



RN 127911-28-8 CAPLUS
CN 1H-Cyclopenta[b]benzofuran-5-acetic acid, 2,3,3a,8b-tetrahydro-2-hydroxy-1-(3-hydroxy-4-methyl-1-octen-6-ynyl)- (9CI) (CA INDEX NAME)



L10 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1990:435308 CAPLUS
DOCUMENT NUMBER: 113:35308

TITLE: Pharmacokinetics and biotransformation of beraprost sodium. VI. Metabolism and excretion of beraprost sodium in dog

AUTHOR(S): Hirano, Yutaka; Matsumoto, Kazuhisa; Tajima, Atsuko; Ohno, Kiyotaka; Yuge, Takuro; Hamasaki, Tadashi; Hase, Toyoji; Horiba, Masahiro

CORPORATE SOURCE: Basic Res. Lab., Toray Ind., Inc., Kamakura, 248, Japan

SOURCE: Yakubutsu Dotai (1989), 4(6), 779-92
CODEN: YADOEL; ISSN: 0916-1139

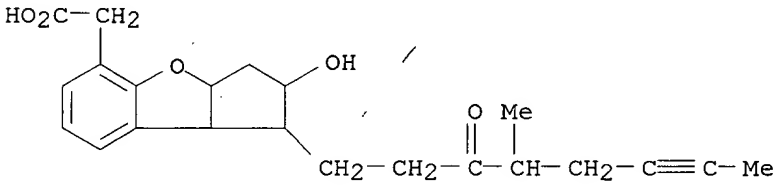
DOCUMENT TYPE: Journal

LANGUAGE: English

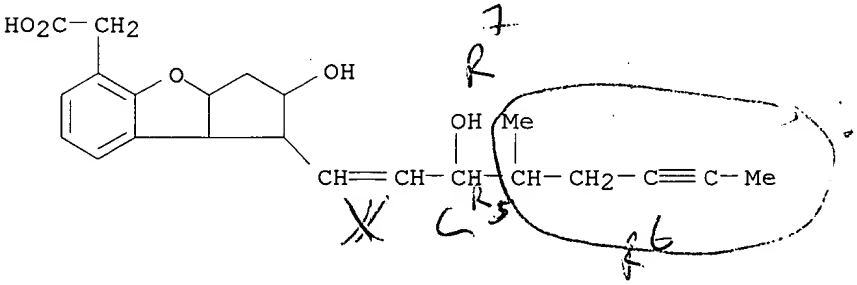
AB The excretion and metab. of beraprost sodium were investigated in dogs after oral administration of 3H-labeled beraprost sodium. In males, the orally administered radioactivity was excreted into urine and feces in 14.7% and 73.8% of administered dose, resp., within 72 h after dosing. In females, 17.6% and 69.6% of the dose were excreted into urine and feces, resp. Beraprost sodium was metabolized by various reactions involving .beta.-oxidn. of the .alpha.-side chain, redn. of the C-13 double bond, oxidn. of the C15 hydroxy group, .omega.-oxidn. of the .omega.-side chain and taurine conjugation. The major metabolites in urine and feces were 2,3-dinor-beraprost and 13,14-dihydro-2,3-dinor-15-oxo-beraprost, accounting for 25.77% and 9.31% of the total dose in males, and 26.80% and 9.80% in females, resp., as detd. by HPLC. Identified metabolites accounted for 67.23% of the dose in males and 68.84% in females, resp. No difference was obsd. in excretion as well as metab. between male and female dogs.

IT **127833-77-6 127911-28-8**
RL: BIOL (Biological study)
(excretion of, to urine and feces, as beraprost metabolite, in dogs, sex in relation to)

RN 127833-77-6 CAPLUS
CN 1H-Cyclopenta[b]benzofuran-5-acetic acid, 2,3,3a,8b-tetrahydro-2-hydroxy-1-(4-methyl-3-oxo-6-octynyl)- (9CI) (CA INDEX NAME)



RN 127911-28-8 CAPLUS
CN 1H-Cyclopenta[b]benzofuran-5-acetic acid, 2,3,3a,8b-tetrahydro-2-hydroxy-1-(3-hydroxy-4-methyl-1-octen-6-ynyl)- (9CI) (CA INDEX NAME)

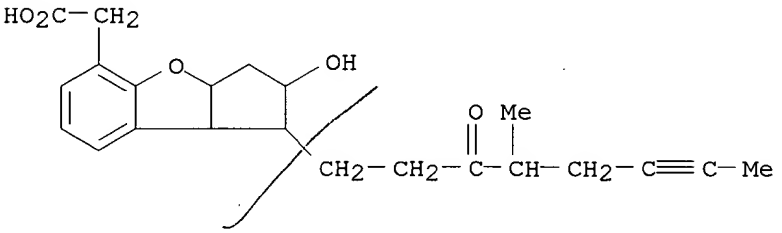


L10 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1990:435307 CAPLUS
DOCUMENT NUMBER: 113:35307
TITLE: Pharmacokinetics and biotransformation of beraprost sodium. V. Plasma level profile of beraprost sodium in dog
AUTHOR(S): Matsumoto, Kazuhisa; Okamoto, Jiro; Hirano, Yutaka; Ohno, Kiyotaka; Yuge, Takuro; Hamasaki, Tadashi; Hase, Toyoji; Horiba, Masahiro
CORPORATE SOURCE: Basic Res. Lab., Toray Ind., Inc., Kamakura, 248, Japan
SOURCE: Yakubutsu Dotai (1989), 4(6), 769-77
CODEN: YADOEL; ISSN: 0916-1139
DOCUMENT TYPE: Journal
LANGUAGE: English

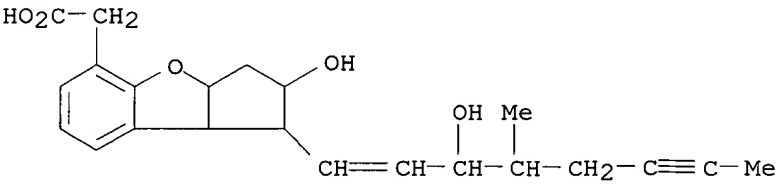
AB The plasma levels of beraprost sodium and its major metabolites were detd. in dogs after oral administration of 3H-labeled beraprost sodium. The major metabolites in the dog plasma were found to be 13,14-dihydro-15-oxo-beraprost, 2,3-dinor-beraprost and 13,14-dihydro-2,3-dinor-15-oxo-beraprost. The plasma concn. of unchanged beraprost sodium increased rapidly, reaching a max. concn. 20 to 25 min in males and 10 to 24 min in females after dosing of 0.008, 0.04 and 0.2 mg/kg, and then declined thereafter with a biphasic pattern. The metabolites appeared in the plasma rapidly after dosing and the major metabolite was 13,14-dihydro-15-oxo-beraprost in both males and females.

IT **127833-77-6 127911-28-8**
RL: BIOL (Biological study)
(formation and pharmacokinetics of, in dogs, sex in relation to)

RN 127833-77-6 CAPLUS
CN 1H-Cyclopenta[b]benzofuran-5-acetic acid, 2,3,3a,8b-tetrahydro-2-hydroxy-1-(4-methyl-3-oxo-6-octynyl)- (9CI) (CA INDEX NAME)



RN 127911-28-8 CAPLUS
CN 1H-Cyclopenta[b]benzofuran-5-acetic acid, 2,3,3a,8b-tetrahydro-2-hydroxy-1-(3-hydroxy-4-methyl-1-octen-6-ynyl)- (9CI) (CA INDEX NAME)



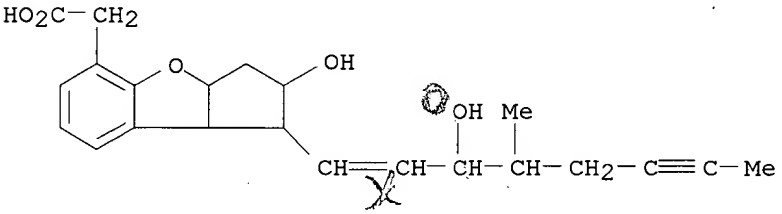
L10 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1990:435306 CAPLUS

DOCUMENT NUMBER: 113:35306
TITLE: Pharmacokinetics and biotransformation of beraprost sodium. IV. Metabolism of beraprost sodium in rat
AUTHOR(S): Matsumoto, Kazuhisa; Tajima, Atsuko; Hirano, Yutaka; Ohno, Kiyotaka; Yuge, Takuro; Hamasaki, Tadashi; Hase, Toyoji; Horiba, Masahiro
CORPORATE SOURCE: Basic Res. Lab., Toray Ind., Inc., Kamakura, 248, Japan
SOURCE: Yakubutsu Dotai (1989), 4(6), 755-68
CODEN: YADOEL; ISSN: 0916-1139
DOCUMENT TYPE: Journal
LANGUAGE: English

AB After oral administration of 3H-beraprost sodium to male rats at a dose of 1.0 mg/kg, metabolites in urine and feces were analyzed by HPLC, and the structures of nine metabolites were detd. by NMR spectroscopy, mass spectrometry and comparative HPLC with synthetic stds. The structures of the metabolites suggest a metabolic pathway of beraprost sodium involving .beta.-oxidn., oxidn. of the hydroxyl group at the C15-position, hydrogenation of the double bond and oxygenation at the .omega.-side chain. A major metabolite in urine and feces was 2,3-dinor-beraprost, a product of .beta.-oxidn. of beraprost sodium (11.26% of the dose in urine and 43.21% of the dose in feces).

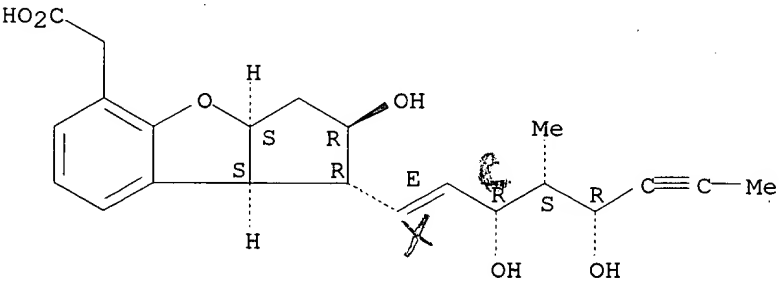
IT **127833-72-1 127833-73-2 127833-74-3 127833-75-4 127833-77-6 127911-26-6 127911-27-7 127911-28-8**
RL: FORM (Formation, nonpreparative)
(formation of, as beraprost metabolite)

RN 127833-72-1 CAPLUS
CN 1H-Cyclopenta[b]benzofuran-5-acetic acid, 2,3,3a,8b-tetrahydro-2-hydroxy-1-(3-hydroxy-4-methyl-1-octen-6-ynyl)- (9CI) (CA INDEX NAME)

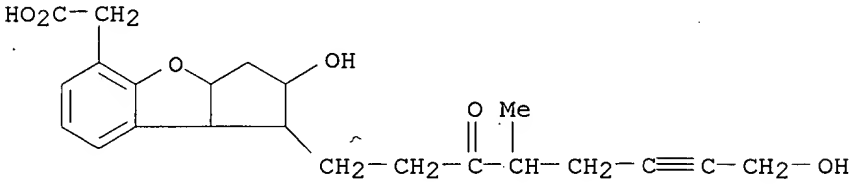


RN 127833-73-2 CAPLUS
CN 1H-Cyclopenta[b]benzofuran-5-acetic acid, 1-(3,5-dihydroxy-4-methyl-1-octen-6-ynyl)-2,3,3a,8b-tetrahydro-2-hydroxy-, [1R-[1.alpha.(1E,3R*,4S*,5R*),2.beta.,3a.alpha.,8b.alpha.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

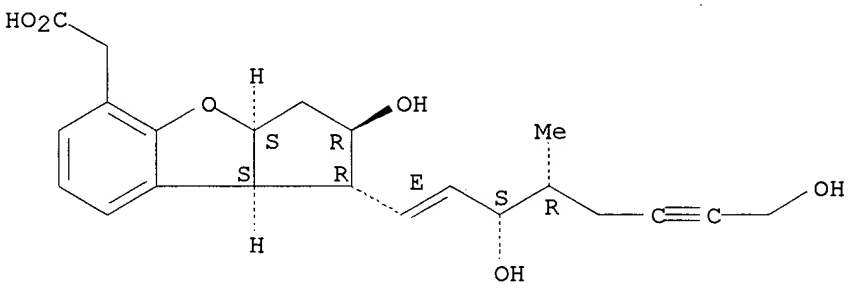


RN 127833-74-3 CAP
CN 1H-Cyclopenta[b]benzofuran-5-acetic acid,
2,3,3a,8b-tetrahydro-2-hydroxy-1-
(8-hydroxy-4-methyl-3-oxo-6-octynyl)-,
[1R-(1.alpha.,2.beta.,3.alpha.,8b.a
lpha.)]- (9CI) (CA INDEX NAME)

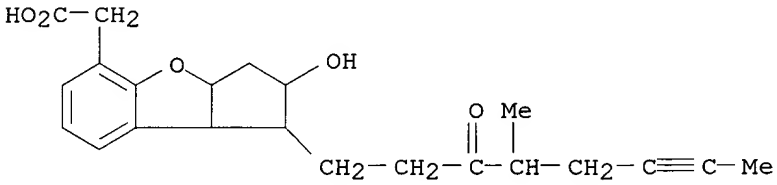


RN 127833-75-4 CAPLUS
CN 1H-Cyclopenta[b]benzofuran-5-acetic acid, 1-(3,8-dihydroxy-4-methyl-1-
octen-6-ynyl)-2,3,3a,8b-tetrahydro-2-hydroxy-, [1R-
[1.alpha.(1E,3S*,4R*),2.beta.,3a.alpha.,8b.alpha.]]- (9CI) (CA INDEX
NAME)

Absolute stereochemistry.
Double bond geometry as shown.

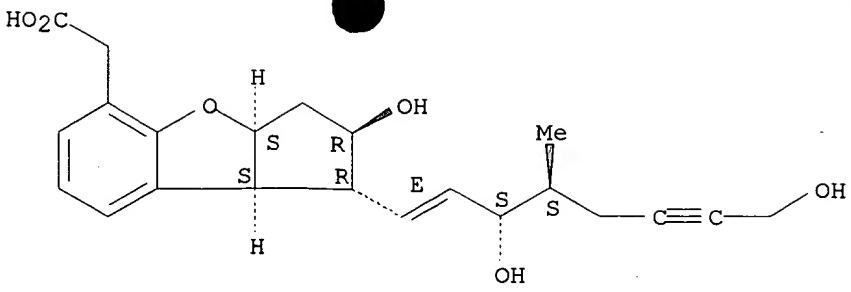


RN 127833-77-6 CAPLUS
CN 1H-Cyclopenta[b]benzofuran-5-acetic acid,
2,3,3a,8b-tetrahydro-2-hydroxy-1-
(4-methyl-3-oxo-6-octynyl)- (9CI) (CA INDEX NAME)

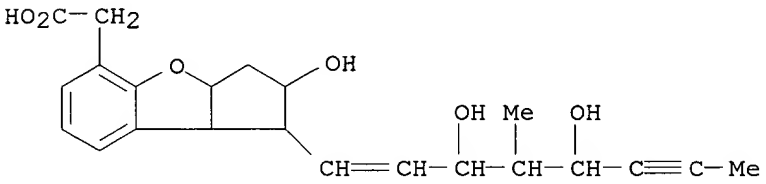


RN 127911-26-6 CAPLUS
CN 1H-Cyclopenta[b]benzofuran-5-acetic acid, 1-(3,8-dihydroxy-4-methyl-1-
octen-6-ynyl)-2,3,3a,8b-tetrahydro-2-hydroxy-, [1R-
[1.alpha.(1E,3S*,4S*),2.beta.,3a.alpha.,8b.alpha.]]- (9CI) (CA INDEX
NAME)

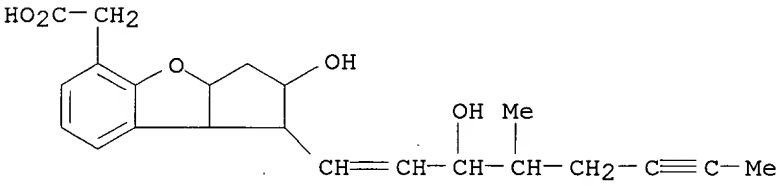
Absolute stereochemistry.
Double bond geometry as shown.



RN 127911-27-7 CAPLUS
CN 1H-Cyclopenta[b]benzofuran-5-acetic acid, 1-(3,5-dihydroxy-4-methyl-1-octen-6-ynyl)-2,3,3a,8b-tetrahydro-2-hydroxy-, [1R-[1.alpha.(1E,3R*,4R*,5R*),2.beta.,3a.alpha.,7b.alpha.]]- (9CI) (CA INDEX NAME)



RN 127911-28-8 CAPLUS
CN 1H-Cyclopenta[b]benzofuran-5-acetic acid, 2,3,3a,8b-tetrahydro-2-hydroxy-1-(3-hydroxy-4-methyl-1-octen-6-ynyl)- (9CI) (CA INDEX NAME)

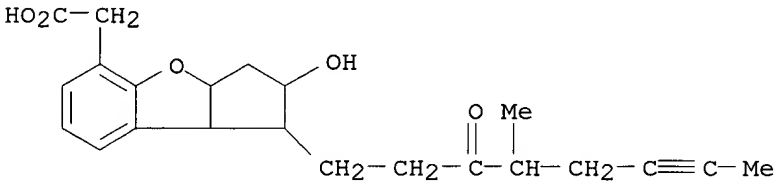


L10 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1990:435305 CAPLUS
DOCUMENT NUMBER: 113:35305
TITLE: Pharmacokinetics and biotransformation of beraprost sodium. III. Metabolites in tissues and enterohepatic circulation of beraprost sodium in rat
AUTHOR(S): Yuge, Takuro; Hamasaki, Tadashi; Tanji, Shoji; Horiba, Masahiro; Matsumoto, Kazuhisa; Tajima, Atsuko; Ohno, Kiyotaka
CORPORATE SOURCE: Cent. Res. Lab., Kaken Pharm. Co., Ltd., Tokyo, 113, Japan
SOURCE: Yakubutsu Dotai (1989), 4(6), 743-53
CODEN: YADOEL; ISSN: 0916-1139
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The metabolites of beraprost sodium in plasma and tissues, and its biliary excretion and enterohepatic circulation were investigated in male and female rats using the 3H-labeled substance. The most predominant metabolite, 2,3-dinor-beraprost, was distributed mainly in the liver and this .beta.-oxidn. metabolite was produced in male rats at an apparently

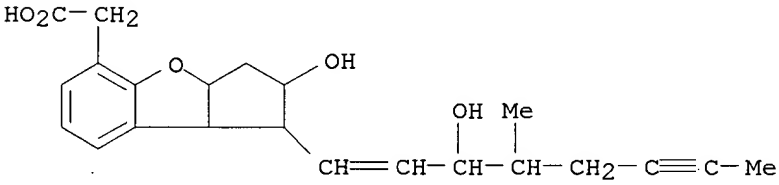
higher level th[redacted]n female rats. On the other [redacted]d, as the oxidn. of the
C-15 alc. was concerned, females possessed higher capacity for this biotransformation process. Anal. of biliary excretion showed that male rats excreted more drug, principally as 2,3-dinor-beraprost, into the bile
than the female rats. This sex difference in biliary excretion was facilitated by enterohepatic circulation. As a result, urinary excretion of beraprost sodium in female rats attained nearly four times that in male
rats. All these results seem to be basically related to the difference in
.beta.-oxidn. capacity in the liver of both sexes.

IT **127833-77-6 127911-28-8**
RL: BIOL (Biological study)
(formation and pharmacokinetics of, sex difference in, liver .beta.-oxidn. and bile secretion in relation to)

RN 127833-77-6 CAPLUS
CN 1H-Cyclopenta[b]benzofuran-5-acetic acid, 2,3,3a,8b-tetrahydro-2-hydroxy-1-(4-methyl-3-oxo-6-octynyl)- (9CI) (CA INDEX NAME)



RN 127911-28-8 CAPLUS
CN 1H-Cyclopenta[b]benzofuran-5-acetic acid, 2,3,3a,8b-tetrahydro-2-hydroxy-1-(3-hydroxy-4-methyl-1-octen-6-ynyl)- (9CI) (CA INDEX NAME)



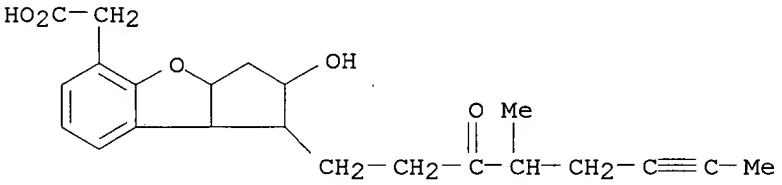
L10 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1990:434325 CAPLUS
DOCUMENT NUMBER: 113:34325
TITLE: Pharmacokinetics and biotransformation of beraprost sodium. I. Plasma level profile of beraprost sodium in rat
AUTHOR(S): Matsumoto, Kazuhisa; Tajima, Atsuko; Hirano, Yutaka; Ohno, Kiyotaka; Yuge, Takuro; Hamasaki, Tadashi; Hase, Toyoji; Horiba, Masahiro
CORPORATE SOURCE: Basic Res. Lab., Toray Ind., Inc., Kamakura, 248, Japan
SOURCE: Yakubutsu Dotai (1989), 4(6), 713-25
CODEN: YADOEL; ISSN: 0916-1139
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Beraprost sodium (TRK-100) (I) labeled with tritium was orally and i.v.

administered to [redacted]le and female rats to examine [redacted] plasma level profile and metab. After oral administration at doses of 0.04, 0.2 and 1.0 mg/kg to male rats, concn. of the unchanged drug achieved max. at 10-30 min (18.4, 42.7 and 220.5 ng/mL, resp.), and then declined biphasically. AUC at a dose of 0.2 mg/kg was 98.2 ng.h/mL which accounted for 81% of AUC after i.v. injection at the same dose. In female rats, higher concns. were obsd. than in the male. Metabolites found in the plasma were 2,3-dinorberaprost, 13,14-dihydro-15-oxoberaprost and 13,14-dihydro-2,3-dinor-15-oxoberaprost. Among the three metabolites, the 2,3-dinorberaprost showed the highest AUC and Cmax, and thus seemed to be a major metabolite of beraprost sodium.

IT **127833-77-6 127911-28-8**
RL: BIOL (Biological study)
(as beraprost metablite)

RN 127833-77-6 CAPLUS
CN 1H-Cyclopenta[b]benzofuran-5-acetic acid, 2,3,3a,8b-tetrahydro-2-hydroxy-1-(4-methyl-3-oxo-6-octynyl)- (9CI) (CA INDEX NAME)



RN 127911-28-8 CAPLUS
CN 1H-Cyclopenta[b]benzofuran-5-acetic acid, 2,3,3a,8b-tetrahydro-2-hydroxy-1-(3-hydroxy-4-methyl-1-octen-6-ynyl)- (9CI) (CA INDEX NAME)